TXR NO. 0050634

April 3, 2002

MEMORANDUM

SUBJECT: ***CARBARYL*** - 3rd Reassessment Report of the FQPA Safety Factor Committee.

NOTE: THIS REPORT REPLACES THE PREVIOUS REPORT OF THE FQPA SAFETY FACTOR COMMITTEE DATED APRIL 30, 2001 (HED DOC. NO. 014553).

FROM: Carol Christensen, Acting Executive Secretary
And
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THROUGH: Ed Zager, Chairman
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PC Code: 056801

The Health Effects Division (HED) FQPA Safety Factor Committee (SFC) met on January 14, 2002 and February 25, 2002 to re-evaluate the hazard and exposure data for Carbaryl with regard to making a decision on the additional safety factor for the protection of infants and children. The SFC determined that reliable data demonstrate that the safety of infants and children will be protected by use of an additional safety factor of 3X. This report replaces the previous report of the FQPA Safety Factor Committee dated April 30, 2001 (HED Doc. No. 014553).

I. HAZARD ASSESSMENT

(*Correspondence:* V. Dobozy to C. Christensen dated February 25, 2002)

Since the last FQPA SFC meeting (April 30, 2001), the toxicology data base for Carbaryl was re-evaluated by the HED Hazard Identification Assessment Review Committee (HIARC) on December 18, 2001 and February 19, 2002.

1. Adequacy of the Toxicology Database

The toxicology data base for Carbaryl is complete for FQPA assessment. There are acceptable guideline developmental studies in the rat and rabbit and a 2-generation reproduction study in rats. The toxicology data base was reviewed by the Hazard Science Assessment Review Committee (HIARC) on July 7, 1998, April 7, 1999, November 2, 1999, March 1, 2001, December 18, 2001 and February 19, 2002.

2. Determination of Susceptibility

There was no evidence of quantitative or qualitative susceptibility following *in utero* exposures in developmental studies in the rat and rabbit.

In the reproduction study, there was evidence of quantitative susceptibility of the offspring. The LOAEL for parental systemic toxicity was based on decreased body weight, weight gain, and food consumption; the NOAEL was 27 mg/kg/day in males and 30 mg/kg/day in females. In the offspring the LOAEL was based on increased numbers of F_2 pups with no milk in the stomach and decreased pup survival; the NOAEL was 5 mg/kg/day in males and 6 mg/kg/day in females. No adverse effects were observed in the reproductive parameters; the NOAEL was the highest dose tested.

In the developmental neurotoxicity study, there was evidence of qualitative susceptibility. For maternal toxicity, the LOAEL was based on decreased body weight gain, alterations in Functional Observational Battery measurements and inhibition of plasma, whole blood and brain cholinesterase activity; the NOAEL was 1 mg/kg/day. For developmental neurotoxicity, the LOAEL was based on the morphometric changes seen in the brain of the offsprings; the NOAEL was 1 mg/kg/day.

3. Degree of Concern and Residual Uncertainties

Since there is evidence of increased susceptibility of the young following exposure to Carbaryl in the 2-generation reproduction study and in the developmental neurotoxicity study, HIARC performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual concerns after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual concerns are identified, HIARC examines whether these residual concerns can

be addressed by a special FQPA safety factor and, if so, the size of the factor needed. The results of the HIARC Degree of Concern analyses for Carbaryl follow.

A. 2-Generation Reproduction Study

The HIARC concluded that there are no residual concerns related to the 2-generation reproduction study because the dose-response for the offspring effects is well-characterized and these effects occurred at a dose level which is above that used for establishing the Chronic Reference Dose (cRfD) for chronic dietary risk assessment.

The HIARC established the Chronic RfD using the LOAEL of 3.1 mg/kg/day in the chronic toxicity study in dogs. Since a NOAEL was not established in this study, an additional uncertainty factor of 3X was applied to the LOAEL (i.e, UF_L). The HIARC determined that 3X is adequate to account for the lack of a NOAEL in this case because: 1) the study was well-conducted and there are sufficient data from subchronic and other chronic studies in other species that support cholinesterase inhibition as the critical effect for Carbaryl; 2.) the data indicate that the dog is more sensitive to the cholinergic effects of Carbaryl and using this species to establish the RfD provides additional protection for the effects seen in the rat (including the reproduction and developmental neurotoxicity studies); 3.) the magnitude of inhibition of plasma cholinesterase inhibition (12-23% decrease) seen in this study was comparable to the magnitude of inhibition (22%) seen in the 5-week study in dogs - indicating no cumulative effect following long-term exposure; 4.) The cholinesterase inhibition seen in females at the LOAEL in this study was not accompanied by clinical signs (response was not judged to be severe); and 5.) no inhibition was seen for any cholinesterase compartment in males at this dose (response was seen in only one sex).

The HIARC concluded that the extrapolated NOAEL of 1 mg/kg/day used to establish the Chronic RfD for Carbaryl is below the NOAEL for offspring toxicity (5 mg/kg/day) in the 2-generation reproduction study and is protective of chronic dietary exposures to infants and children.

B. Developmental Neurotoxicity Study

The HIARC concluded that there was a low level of concern for the developmental effects seen in the developmental neurotoxicity study and no residual uncertainties with respect to this study based on the following evidence:

- Any concern for the lack of brain morphometric measurements in the offspring at the mid-dose (1 mg/kg/day) was negated since even at the high dose of 10 mg/kg/day, the morphometric changes were minimal and therefore, it is unlikely that adverse effects would be seen at the mid-dose level (1 mg/kg/day - 10% of the LOAEL).

- Any concern for the lack of comparative data in adults and offspring for cholinesterase inhibition was negated since no FOB alterations were seen in pups.

Other studies in the data base show that when cholinesterase inhibition was seen in adult animals, it usually was accompanied by FOB alterations. Additionally, the results of the National Institute for Environmental Health Sciences study (discussed below) indicate that there is no difference in cholinesterase inhibition in pups and adults. The dose-related decrease in cholinesterase activity in the brain and blood of dams at gestation day 19 was very similar to the fetal brain cholinesterase levels taken at the same time.

The HIARC established the Acute RfD for Carbaryl using the NOAEL of 1 mg/kg/day in the developmental neurotoxicity study in rats which is protective of single dose exposures to infants and children.

4. Summary of Open Literature Findings

In the scientific literature, there are two relatively recent studies which demonstrated effects on sperm at high doses (50 and 100 mg/kg/day) of Carbaryl. The results of these two studies indicated that Carbaryl caused weight reductions in the testes, epididymides, seminal vesicles, prostate and coagulating glands of young rats; changes in testicular enzymes; decreased sperm counts and sperm motility; increased sperm morphological abnormalities; and moderate atrophy of seminiferous tubules of the testes.

In a published developmental study in Fisher 344 rats conducted by EPA's Health Effects Research Laboratory, Carbaryl was administered from gestation day 6 through 19 at doses of 78 or 104 mg/kg/day. Clinical signs related to cholinesterase inhibition (tremor, motor depression, jaw clonus and lacrimation) were observed in dams but it is unclear if they occurred at both dose levels. There was also increased prenatal mortality at the high dose (104 mg/kg/day) and decreased pup weights at the low (78 mg/kg/day) doses.

In an unpublished developmental neurotoxicity study in SD rats from the National Health and Ecological Effects Research Laboratories at EPA and the National Institute for Environmental Health Sciences/National Toxicology Program Carbaryl was administered by gavage at doses of 0, 6, 12 or 25 mg/kg/day. The chemical or its metabolite 1-naphthol was not present in pups' plasma above the limit of detection at any exposure concentration (0, 6, 12 or 25 mg/kg/day). There was a dose-related decrease in ChE activity in the brain and blood of dams at GD 19, and fetuses taken at that time also showed a very similar level of inhibition in fetal brain cholinesterase. There was a decrease in the number of live pups/litter at the high dose. There were no changes in cognitive function. Equivocal changes in Functional Observational Battery parameters were observed in male and female offspring.

II. EXPOSURE ASSESSMENT

1. Dietary (Food) Exposure Considerations
(*Correspondence:* V. Dobozy to C. Christensen dated January 7, 2002)

Carbaryl is used late in the season at maximum seasonal rates of 6 -12 lb of active ingredient (a.i.) per acre. Pre-harvest intervals (PHIs) range from 1-29 days, but most PHIs are one week or less. Single application rates are 1-5 lb ai/A with repeated applications on a weekly basis. U.S. tolerances range from 10-100 ppm. Codex MRLs have been established for numerous commodities, including fruits, grains, forage/fodder, and livestock commodities. The limits range from 0.1/0.5 for livestock commodities to 100 ppm for forage/hay. Most fruit and vegetable limits range from 1 to 10 ppm.

Carbaryl is registered for use on almost all crop groups and miscellaneous commodities including pome fruit, stone fruit, legumes, cereal grains and fruiting vegetables. Residues are expected in meat and milk. The qualitative nature of the residue of Carbaryl in plants and animals is adequately understood. Based on the results of plant and animal metabolism studies, the HED Metabolism Committee concluded that the Carbaryl residue to be regulated in plants is Carbaryl *per se* (DP Barcode D221979, S. Hummel, 2/8/96). The Metabolism Committee also concluded that the residues of concern in meat and milk are the free and conjugated forms of Carbaryl, 5,6-dihydro-5,6-dihydroxy carbaryl, and 5-methoxy-6-hydroxy carbaryl (C. Olinger, D255855, 6/21/99). Residues are primarily surface residues**.**

DEEM analyses are being conducted at the highest level of refinement available (Tier IV). Adequate PDP and FDA monitoring data are available for the vast majority (>80%) of the commodities. These commodities include those which are considered to be significant in the diets of children such as apples, potatoes, carrots, succulent beans, soybean, orange, orange juice, apple, apple juice, pear, peach, wheat, banana, grape, grape juice and milk. For those commodities not monitored by FDA and PDP, field trial data will be used. These include garden beets, turnips, mustards, dried beans, almonds, pecans, walnuts, field corn grain, rice, flax seed, okra, olive, peanuts, pistachio, and sunflower. Carbaryl residues from field trials were <LOQ in/on sweet potato, sugar beets, corn grain, flax seed, and peanuts. Quantifiable residues were detected in all other raw agricultural commodities (RACs). For a given crop, residue levels were quite variable overall, probably owing to climactic variations, but were generally consistent within any specific field trial location. Percent of crop treated will also be incorporated. Crops with the highest percent of the crop treated include apples, (30%), avocados (85%), blueberries(45%), cherries (36%), asparagus (87%), among others. Carbamate market basket data are also available for the commodities, orange, apple, peach, broccoli, lettuce, tomato, bananas, and grapes.

Additional data were required for the dermal use of Carbaryl on poultry and its use in poultry houses; however, the registrant has stated that they are no longer supporting these uses. In the previously conducted dietary assessment, the current tolerance for poultry was used, and as a result, poultry was determined to be a significant contributor to the risk estimate. When poultry is not included in the diet, the results of the Critical

Exposure Contribution analysis showed no specific commodity comprised a large percentage of the residues found in the tail end of acute exposure.

2. Dietary (Drinking Water) Exposure Considerations
(*Correspondence:* V. Dobozy to C. Christensen dated January 7, 2002)

The environmental fate data base for Carbaryl is adequate for the characterization of drinking water exposure. Fate data indicate that parent Carbaryl and its degradate 1-naphthol are fairly mobile and slightly persistent. In general they are not likely to persist or accumulate in the environment, however, under acidic conditions with limited microbial activity they may persist.

Because of the relatively limited persistence of the compound in the environment it is unlikely that non-targeted monitoring studies will detect the maximum concentrations that occur. Some non-targeted monitoring data are available but are of limited utility in developing EECs for ecological and human health risk assessment. Therefore modeling was used to estimate surface water and groundwater concentrations that could be expected from normal agricultural use. The results of the modeling are supported by the available monitoring data.

For developing surface water, EECs computer modeling with the EPA PRZM3.12 and EXAMS 2.97.7 programs were used to estimate the concentration of Carbaryl in surface water. Index reservoir scenarios corrected for Percent Cropped Area (PCA) for representative crops were used. SCI-GROW was used to calculate a groundwater screening exposure value to be used in determining the potential risk to human health.

3. Residential Exposure Considerations
(*Correspondence:* V. Dobozy to C. Christensen dated January 7, 2002)

Carbaryl is currently registered for many residential uses. Homeowner handler exposure scenarios exist for a variety of use patterns including applications of dusts to vegetables, ornamentals, and pets (dogs & cats); applications of ready-to-use products for nuisance insect control; applications of liquid sprays with a variety of hand equipment to gardens, trees, vegetables, and turf; and applications of granular formulations to turf. Carbaryl can be used in outdoor residential areas and to treat pets. Therefore, a number of residential post-application exposure scenarios exist for toddlers and children.

Several chemical- and scenario-specific studies designed to quantify exposures to homeowner applicators are available. There are a number of dislodgeable foliar residue studies for Carbaryl that have been used for home gardening activities. Also, there are TTR data from 3 sites (CA, PA, GA) that have been used for the dermal risk assessments (i.e., transferability is >1%). Mouthing behaviors have been addressed using the new 5% factor for wet hands and not the TTRs as stipulated in the latest updates to the Residential SOPs. These data will be used, where appropriate, to calculate residue concentrations

and exposures over time instead of using the Agency default assumptions. In addition, the latest Outdoor Residential Exposure Task Force (ORETF) data for homeowner applications to turf have been used which are also the same values that have been incorporated in the Residential SOPs. For any other remaining scenarios not addressed by the Aventis or ORETF data, PHED or the Residential SOPs were used.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendations

The FQPA SFC recommends that OPP depart from the default 10X additional safety factor and instead use a different additional safety factor of 3X. This recommendation is based on reliable data supporting the findings set forth below.

A. Traditional Additional Safety Factor (Addressing Data Deficiencies)

The FQPA SFC concurs with the HIARC recommendation for the use of a 3X additional safety factor to address the use of a LOAEL in establishing the Acute and Chronic RfDs, and the toxicity endpoints selected to assess short- and long-term residential exposure scenarios (oral, dermal, and inhalation). The rationale as to why reliable data support the safety of using a 3X to address this data deficiency is discussed above in Section I.3.

B. Special FQPA Safety Factors

Taking into account the HIARC recommendation regarding the data deficiency, the FQPA SFC recommends that no Special FQPA Safety Factor is necessary to protect the safety of infants and children in assessing Carbaryl exposure and risks.

2. Rationale and Findings Regarding Recommendation on Special FQPA Safety Factor

The Committee concluded that no Special FQPA safety factor was needed because:

The toxicology database is complete and there is no quantitative or qualitative evidence of increased susceptibility in rat or rabbit fetuses following *in utero* in the standard developmental studies. Although there is evidence of qualitative susceptibility developmental neurotoxicity study, HIARC concluded there is a low level of concern for the effects in the developmental neurotoxicity study, as discussed in Section I.3. The RfDs established would account for any uncertainties and are protective of pre-pre/postnatal toxicity following acute and chronic exposures. Similarly, although there is evidence of increased susceptibility in the offspring in the 2-generation reproduction study, there are no residual uncertainties (Refer to Section I.3.). The chronic RfD would be protective of the pre-pre/post natal toxicity following chronic dietary exposures. The

doses/endpoints selected for residential exposures, are also protective of any pre-pre/post natal toxicity resulting from non-dietary exposures.

There are no residual uncertainties identified in the exposure databases. The dietary food exposure assessment utilizes estimates derived from monitoring data (PDP, FDA), the carbamate market basket survey, percent crop treated information (as applicable), and processing data. The dietary drinking water assessment includes a complete environmental fate database for both the parent and the major metabolite (1-napthol) and uses modeling results based on detailed chemical-specific data. The modeling results are supported by drinking water monitoring data and do not underestimate the exposure and risks posed by Carbaryl. The residential exposure assessment includes chemical-specific dislodgeable foliar residue studies (DFRs), ORETF data, a registrant submitted use and usage study, and chemical-specific total transferable residue (TTR) studies for the handler and post-application scenarios. In addition, there are human biomonitoring data to support the results of the residential exposure estimate.

3. Application of the FQPA Safety Factors (Population Subgroups / Risk Assessment Scenarios)

The FQPA safety factor recommendation is for a 3X traditional safety factor to address data deficiencies and no additional Special FQPA safety factor. The 3X traditional safety factor should be applied to the Chronic RfD and to long-term residential exposure scenarios (dermal, and inhalation). No other FQPA safety factor would be appropriate for Carbaryl.

4. Summary of FQPA Safety Factors

Summary of FQPA Safety Factors for Carbaryl				
	LOAEL to NOAEL (UF_L)	**Subchronic to Chronic (UF_S)**	**Incomplete Database (UF_{DB})**	**Special FQPA Safety Factor (Hazard and Exposure)**
Magnitude of Factor	**3X**	1X	1X	**1X**
Rationale for the Factor	**Use of a LOAEL to establish toxicity endpoint (i.e, a NOAEL was not identified in the critical study). Refer to Section I.3.**	No subchronic to Chronic extrapolations performed	Toxicity Database is complete	**No residual concerns regarding pre- or post-natal toxicity or completeness of the toxicity or exposure databases**
Endpoints to which the Factor is Applied	**Chronic dietary and Long-term residential exposures (Dermal and Inhalation)**	Not Applicable	Not Applicable	**Not Applicable**